The standard for determining whether the specification meets the enablement requirement was set forth in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? In In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir. 1988), the Court held that the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed," and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. The Wands Court further listed eight factors for enablement analysis:

1) The breadth of the claims;
2) The nature of the invention;
3) The state of the prior art;
4) The level of one of ordinary skill;
5) The level of predictability in the art;
6) The amount of direction provided by the inventor;
7) The existence of working example; and
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, considering all the Wards' factors, particularly applicants' detailed disclosure, coupled with the state of the art at the time of patent filing, applicants respectfully traverse the rejection on the basis that the claims are fully enabled for their entire scope.

Applicant's Claims Are Fully Enabled

Far from being directed to paclitaxel and albumin as alleged by the Examiner, applicants' specification provides a detailed description how to make and use of compounds that are commensurate with the claim scope, for example, the specification discloses:

1) the use of human albumin (different concentrations and different sources) and human gamma globulin (page 15, lines 30-40);
2) example II.4 further discloses the preparation of a pharmaceutical formulation for parenteral use comprising human gamma globulin in controlled aggregation state

solution with paclitaxel. Example II.4 further discloses the binding using UF filtrate of HPLC method and LC/MS as well as using ultrafiltration to measure denatruation (page 17-18, example II.4);
3) example II.22 further discloses similar methods for preparing a pharmaceutical formulation using animal serum albumin, immunoglobulin, glycoproteins, interferons and interleukins (page 19, lines 25-27);
4) example II.24 further discloses the preparation of a pharmaceutical formulation using amphotericin B with human serum albumin (page 20, example II.24);
5) example II.25 further discloses the preparation of a pharmaceutical formulation of recombinant human serum albumin and amphotericin B (page 20, example II.25);
6) example II.26 further discloses the preparation of a pharmaceutical formulation of human serum albumin and camptothecin (page 21, example 22.26);
7) example II.27 further discloses the preparation of a pharmaceutical formulation of recombinant human serum albumin and camptothecin (page 21, example II.27);
8) example II.29 further discloses the preparation of a pharmaceutical formulation of human serum albumin and carbamazepin (page 22, example II.29);
9) example II.30 further discloses the preparation of a pharmaceutical formulation of human serum albumin and cyclosporine A (page 23, example II.30);
10) example II.31 further discloses the preparation of a pharmaceutical formulation recombinant human serum albumin and cyclosporine A (page 23, example II.31);
11) example II.32 further discloses the binding of human gamma globulin with cyclosporine A (page 23, example II.32);
12) example II.33 further discloses the preparation of a pharmaceutical formulation of human serum albumin and propofol (page 24, example II.23);
13) example II.34 further discloses the preparation of a pharmaceutical formulation of recombinant human serum albumin and propofol (page 25, example II.34); and
14) example II.35 further discloses the preparation of a pharmaceutical formulation of human serum albumin and amphotericin B (page 25, example II.35).

The specification further instructs those skilled in the art how to make the pharmaceutical formulation solution for amphotericin B, camptothecin, carbamazepine, cyclosporin A, paclitaxel and propofol (page 26, lines 10-14). In addition, the specification describes various methods to conduct in vitro studies; for example, i) colony growth inhibition assay (page 27, line 4 to page 29, line4); ii) in vivo pharmacokinetic test page 29 (lines 4-page 30, line 29); iii) hypersensitivity tests (page 30, lines 37- page31, line 19); and iv) quantitative assay of chromatin activation of blood lymphocytes (page 31, lines 20-26).

It is well settled that an applicant needs not make or test all embodiments of the invention in order to meet the requirement of 35 U.S.C. §112. So long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, the enablement requirement of 35 U.S.C. §112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

The Examiner has already conceded that the specification enables the invention for at least paclitaxel and albumin. Because the present specification further provides detailed instructions of how to make and use other therapeutical active drugs including amphotericin B, camptothecin, carbamazepine, cyclosporin A, propofol and other plasma proteins including recombinant human serum albumin, human serum albumin and human gamma globulin, applicants respectfully submits that the present specification fully enables the full scope of the claims.

For the foregoing reasons, Applicant believes that the ground for the rejection has been negated. Accordingly, the Examiner's withdrawal of the rejection is earnestly solicited.

Rejection of Claims 30-37, 42-90 and 93-94 Under 35 § U.S.C. 112, First Paragraph

Claims 42, 81-90 and 93-94 have been cancelled by this amendment, without prejudice; thus mooting their rejection. New claims 95-102 (replacing claims 30-37) and 103-140 (replacing claims 43-80) have been added respectively, upon which applicants respectfully address their rejection as follows.

New claim 95 has now been amended to recite a pharmaceutical composition for parenteral use having i) an aqueous solution including; ii) a therapeutically active drug with low aqueous solubility; and ii) a plasma protein non-covalently bound to the therapeutic active drug.

Accordingly, applicants believe that the amendments should provide adequate limitations in commensurate with the breadth of the claims.

Rejection of Claims 30-37 Under 35 U.S.C. § 112, Second Paragraph

New claims 95-102 are added to replace claims 30-37. New claims do not recite the term "substantial binding affinity." As such, the rejection should be overcome.

Rejection of Claims 42-80 Remain Rejected Under 35 U.S.C. § 112, First Paragraph

Claim 42 has been cancelled and the rejection is mooted. New claims 103-140 are added to replace claims 43-80.

Applicants respectfully that the new claims have been amended to better clarify the claimed invention. As such, applicants submit that new claims 103-140 are not vague and confusing.

Rejection of Claims 30-31 and 36 under 35 U.S.C. 102(b) or Alternatively, 103(a) As Being Anticipated By Satoh (EPO 0326618, 1988)

New claims 95-96 and 101 are added to replace claims 30-31 and 36, respectively.

New claims 95-96 and 101 have been amended to explicitly recite "A pharmaceutical formulation for parenteral use, comprising: i) an aqueous solution including ii) a therapeutically

active drug . . .; and iii) a plasma protein . . . non-covalent bound to the therapeutically active drug."

As stated in our September 18, 2000 Amendment, Satoh merely discloses aqueous **suspensions,** but not true clear aqueous **solutions** suitable for parenteral administration. Satoh's composition, when administered in liquid form, are suspensions (Satoh, page 12, lines 6-9). Satoh's formulations are not even completely dissolved during the manufacturing process (Satoh, page 12, lines 6-9). Parental administration, for obvious reasons, requires a formulation of completely dissolved components. Satoh makes no suggestion as to making a formulation comprising completely dissolved components. Neither does Satoh make any suggestion as to making a pharmaceutical formulation suitable for parenteral administration. As such, Satoh does not anticipate the pending claims, nor renders the pending claims obvious.

Rejection of Claims 30, 42-90 and 93-94 under 35 U.S.C. 112, First Paragraph

Claims 42, 81-90 and 93-94 have been cancelled by this amendment, without prejudice; thus mooting their rejection. New claims 95 (replacing claim 30) and 103-140 (replacing claims 43-80) have been added respectively.

The new claims do not recite the following terms:

i) "a water-soluble product or pharmaceutical formulations in solid or liquid for and their organic solvent free true aqueous solution";
ii) ". . . substantially binding affinity to plasma protein, in an interlinked state with a plasma protein fraction . . .";
iii) "optionally";
iv) "preferably";
v) "characterized";
vi) "a pharmaceutical formulation ... having a solid state or the form of an aqueous solution"; and
vii) "and/or".

As such, applicants believe that the new claims should overcome the rejection.

CONCLUSION

In view of the foregoing, Applicants submit that all of the pending claims of the subject application are now in condition for allowance, and issuance of a Notice of Allowance is respectfully requested. The Examiner is invited to telephone the undersigned attorney at (212) 908-6018, if there are any questions concerning this amendment.

Respectfully submitted,

Date: June 18, 2002

Siu K. Lo
Reg. No. 46,877

Marked Up Version to Show Changes

Paragraph 1 appearing at page 10, lines 11-29.

The proper way to best eliminate the organic solvent depends on the active substance and on the protein involved. It follows that from the nature of the active product (the pair including the active substance and the protein) that the methods applied have to ensure mild conditions. Lyophilization leads to homogenous, solid state water-soluble products which on redissolution in water can be administered [intraperitonially] parenterally. It might be advantageous to combine the above steps e.g. to make the process more economical by first preparing a concentrate of the active substance/protein pair and thereafter subjecting said concentrate to lyophilisation. Some of the active substance/protein pairs (e.g. the pair amphothericin B/serum albumin) can be successfully concentrated by way of ultrafiltration or dialysis. Some other pairs (e.g. paclitaxel/HSA) are preferably treated by way of lyophylisation. Some pairs should first be ultrafiltrated and the concentrate obtained should then be subjected to lyophilisation.